Clinical Protocol

Protocol Title: **An Open-Label Study to Evaluate the Safety of Teplizumab (PRV-031) in At-Risk Relatives Who Develop Type 1 Diabetes**

Protocol Number: PRV-031-002

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Compound: **Teplizumab**

Study Phase: 2

Short Title: At-Risk Extension

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1. Protocol Summary

1.1. Synopsis

Protocol Title: An Open-Label Study to Evaluate the Safety of Teplizumab (PRV-031) in At-Risk Relatives Who Develop Type 1 Diabetes

Short Title: At-Risk Treatment Protocol

Rationale:
Teplizumab (also known as PRV-031, hOKT3γ1 [Ala-Ala], and MGA031) is a humanized 150-kilodalton monoclonal antibody (mAb) that binds to the CD3-ε epitope of the T cell receptor. A recently completed TrialNet study (TN-10) demonstrated that teplizumab significantly delayed the onset of clinical diabetes in relatives at very high risk for type 1 diabetes (T1D). As teplizumab is predicted to preserve beta cell function, participants who were in the TN-10 trial and have subsequently developed clinical T1D after the conclusion of that trial, are eligible to enroll and receive teplizumab treatment in this open-label study within one year of their clinical T1D diagnosis.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of teplizumab treatment, administered intravenously (IV) to participants in the TN-10 trial who have developed T1D.	• Incidence of treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs)
Secondary	
• To evaluate the pharmacokinetics (PK) and immunogenicity of teplizumab • To evaluate whether teplizumab treatment reduces the loss of β cells, over 78 weeks (18 months), in individuals with recent diagnosis of T1D. • To evaluate key clinical parameters of diabetes management, including insulin use, hemoglobin A1c (HbA1c), and clinically important hypoglycemic episodes over 78 weeks	• Levels of teplizumab in the serum and anti-drug antibodies • The area under the time-versus-concentration curve (AUC) of C-peptide after a 4-hour (4h) mixed-meal tolerance test (MMTT), a measure of endogenous insulin production and β cell function, over 78 weeks • HbA1c levels; insulin use, defined as a daily average dose in units per kilogram per day (U/kg/day); and frequency of clinically important hypoglycemic episodes over 78 weeks

Objectives	Endpoints
• To evaluate whether treatment with teplizumab increases the frequency of exhausted T cells	• Frequency of CD8+ TIGIT+ KLRG1+ T cells

Overall Design

The study is a single-arm, multicenter, open-label clinical trial.

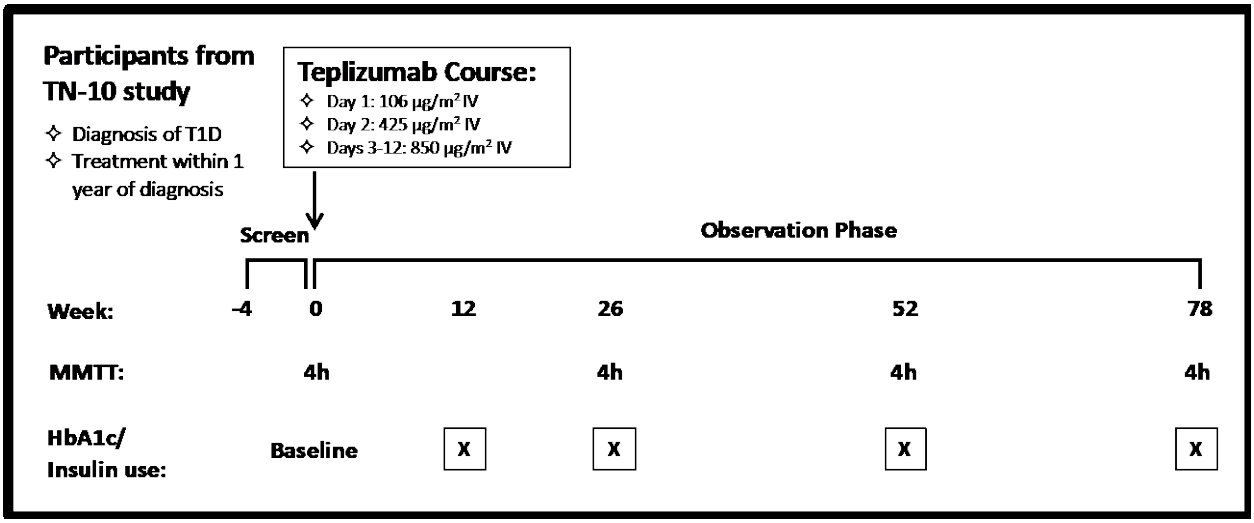
Teplizumab-treated and placebo participants who were in the TrialNet TN-10 trial, have been diagnosed with T1D, and are able to start teplizumab treatment within 1 year of the T1D diagnosis are eligible to enroll in this open-label study.

Number of Participants:
Up to 30 participants may be enrolled in this study.

Treatment and Study Duration:
All participants will receive a 12-day course of teplizumab given through daily IV infusion. Participants will have a screening period of up to 4 weeks, a treatment period of 12 days, and a follow-up period of up to 78 weeks (18 months) from the first dose of treatment.

1.2. Schema

The study schema is noted below.



1.3. Schedule of Events

Week	**-4**	**1**							**2**					**4**	**12**	**26**	**52**	**78**	**ET**
Month	**-1**	**1**													**3**	**6**	**12**	**18**	**ET**
Day	**Screen[1]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**28**	**84**	**182**	**364**	**546**	**ET**
Visit window		*Not applicable*												*±4 days*	*±4 days*	*±2 wks*	*±2 wks*	*±2 wks*	
Visit number	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**ET**
Informed consent/assent	X																		
Inclusion/exclusion criteria review	X	X																	
Medical history	X	X	X	X	X			X					X		X	X	X	X	X
Height (cm) & weight (kg)	X	X															X	X	X
Vital signs[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam (C=Complete; P=Partial)	C	P												P	P	P	P	P	C
Previous/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Teplizumab dose calculation		X																	
Premedication		X	X	X	X	X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]						
Teplizumab administration[4]		X	X	X	X	X	X	X	X	X	X	X	X						
Tuberculosis testing (PPD or IGRA)	X																		
Chemistry and LFTs[5,6]	X	X	X						X				X	X	X	X	X	X	X
CBC with differential and platelets[5]	X	X	X	X	X		X		X				X	X		X	X	X	X
Teplizumab levels[7]		X			X					X			X	X		X	X		X
Anti-teplizumab antibodies[7]		X			X					X			X	X		X	X		X
EBV/CMV serology[8]	X																		
EBV and CMV viral loads[8]	X													X	X				
HIV, HBV, HCV serology[8]	X																		
4h MMTT[9]		X														X	X	X	X
T1D autoantibodies	X																		
Urine pregnancy test (WOCBP only)	X	X					X						X			X	X	X	X
Urine ketones[10]																			
HbA1c	X														X	X	X	X	X
Mechanistic assessments[11]	X	X											X		X	X	X	X	X

Abbreviations: ALT=alanine aminotransferase, AST=aspartate aminotransferase, BP=blood pressure, BUN=blood urea nitrogen, CBC=complete blood count, CMV=cytomegalovirus, EBV=Epstein-Barr virus, EBNA=Epstein-Barr nuclear antigen, ET=early termination visit, HbA1c=hemoglobin A1c, HBV=hepatitis B virus,

HCV=hepatitis C virus, HIV=human immunodeficiency virus, Ig=immunoglobulin IGRA= interferon-gamma release assay, LDH=lactate dehydrogenase, MMTT= mixed-meal tolerance test, PPD=purified protein derivative, T1D=type 1 diabetes, WOCBP=women of childbearing potential

Footnotes:

1. Enrollment must occur within 4 weeks of screening.
2. Vital signs include temperature, pulse, blood pressure, and respiration. On dosing days, vital signs should be collected pre-dose, 15 minutes after the start of infusion, at the end of infusion, and 60 minutes after the end of infusion.
3. Pre-treatment medications are required on Days 1-5, optional on Days 6-12.
4. Teplizumab dose: Day 1: 106 $\mu g/m^2$, Day 2: 425 $\mu g/m^2$, Days 3 to 12: 850 $\mu g/m^2$ daily.
5. These results must be reviewed prior to drug administration (see Section 8.1.2). CBC with differentials are done locally.
6. Liver function tests (ALT, AST, LDH, alkaline phosphatase, total protein, albumin, total and direct bilirubin) and chemistries (sodium, potassium, chloride, CO_2, glucose, BUN, creatine) are done locally. Day 1 samples should be obtained pre-dose.
7. Blood samples for the measurements of teplizumab trough levels and anti-drug antibodies are to be obtained within 30 minutes before study drug infusion.
8. Serology assessments include EBV IgG and IgM, EBNA, CMV IgG and IgM, HIV, HBV, and HCV are done locally. All participants, regardless of whether they are seropositive or seronegative for EBV and CMV at screening, will be tested for viral load by the central lab at the indicated visits.
9. MMTT: 4-hour samples should be collected pre-dose on Day 1. Samples will be archived for possible future pro-insulin analysis.
10. In participants who have discontinued insulin therapy, urine ketones should be checked once daily.
11. Includes samples for RNA, plasma, serum, DNA, and measurements of B and T cell numbers and function to understand the effect of therapy on the immune system and infectious disease. Day 1 samples should be obtained pre-dose.

2. Introduction

2.1. Type 1 Diabetes (T1D)

2.1.1. Definition and metabolic characteristics of Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1D) is an immune-mediated disease in which insulin-producing beta cells are completely or near completely destroyed, resulting in life-long dependence on exogenous insulin. It is a chronic and potentially disabling disease that represents a major public health and clinical concern. The number of patients being diagnosed with type 1 diabetes is increasing each year and is approaching an epidemic level in some countries that track this information (Imperatore 2018, EURODIAB 2000).

Compared to individuals with the more common form of diabetes, Type 2 diabetes, the metabolic impairment in T1D is much more severe and the loss of insulin production more complete. Continuous exogenous insulin therapy is needed to prevent ketoacidosis and allow assimilation of food and to maintain life. Most likely as a consequence of the absolute deficiency of insulin, glucose counter regulation (i.e. the hormonal response to insulin induced hypoglycemia) is impaired, and therefore, hypoglycemia is a frequent complication of the disease. The occurrence of hypoglycemia limits the ability to achieve near normal glucose control. The Diabetes Control and Complications Trial (DCCT) showed that the long-term complications could be reduced with near normal control of glucose levels but at the cost of an increased frequency of severe hypoglycemia (DCCT 1993). While there have been significant improvements in insulin delivery systems, such as continuous subcutaneous insulin infusions with insulin pumps, normal glucose control, particularly in children, is rarely achieved. Individuals with Type 1 diabetes remain at risk for secondary end-organ complications including visual impairment and blindness, renal failure, vascular disease and limb amputation, peripheral neuropathy, stroke, acute risk for severe hypoglycemia, and others. Moreover, at the time of diagnosis, many individuals, and children in particular, suffer significant morbidity frequently requiring intensive care admission. Contemporary clinical data support the need for prevention of T1D: two recent studies identified loss of 17.7 and 14.2 life-years among men and women, respectively, who were diagnosed as children before age 10, and 11 and 13 life-years lost for Scottish men and women diagnosed before age 20 (Livingstone 2015, Rawshani 2018). Prevention of T1D remains, therefore, an important unmet medical need.

2.1.2. Natural History of Type 1 Diabetes

Much is known about the natural history of the T1D disease process (Atkinson 2005). Although all people are susceptible, relatives of individuals with T1D are at much greater risk for development of the disease. In the general population, approximately 0.3 % of individuals will develop T1D. In contrast, those with a relative with T1D have a 5% incidence of disease – a 15-fold increase (Riley 1990). Further risk stratification among family members depends upon genetic, immune and metabolic data (Sherr 2008).

In genetically susceptible persons, T1D progresses through asymptomatic stages prior to the development of overt hyperglycemia. These stages are characterized by the appearance of autoantibodies (Stage 1) and then dysglycemia (Stage 2). In Stage 2, metabolic responses to a glucose load are impaired but other metabolic indices, for example, glycosylated hemoglobin, remain normal, and insulin treatment is not needed (Riley 1990). These immunologic and metabolic features can identify persons at high-risk for development of clinical disease; overt hyperglycemia, once it develops (Stage 3), requires insulin treatment.

Based on data from the Diabetes Prevention Trial, type 1 diabetes (DPT-1) and other natural history studies, the risk for developing diabetes in relatives without the disease can be defined by the presence of autoantibodies and the degree of metabolic impairment (Sosenko 2006). Autoantibody positive subjects enrolled in the DPT-1 study who had impaired or indeterminate glucose tolerance (ie, a glucose level after ingestion of oral glucose of > 200 mg/dL before 120 min, and/or a glucose level at 120min 140-200 mg/dL and/or fasting glucose between 110 and 126 mg/dL) were at very high risk (78% over 5 years) of developing T1D over a follow-up period of 5 to 6 years. Similar results confirming the very high risk of those with abnormal glucose were found in the ENDIT (European Nicotinamide Diabetes Intervention Trial) study in which nicotinamide failed to prevent the onset of diabetes in relatives at risk for the disease (Gale 2004). The results of the recently completed study, "Anti-CD3 Monoclonal Antibody (Teplizumab) for Prevention of Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus" (TrialNet TN-10) confirmed this high risk: The median time to diagnosis of T1D in the high-risk group with these clinical features was 24.4 months. In the TN-10 study there was a decline in the ability to make insulin in the placebo-treated participants. The mean (standard deviation [SD]) decline in the insulin secretory capacity (calculated from a 2-compartment model and adjusted for age and body surface area) was 44061±253 (SD) pmol/ml/120 min (n=30).

2.2. Teplizumab Overview

The Fc-engineered teplizumab [hOKT3γ1 (Ala-Ala)] was developed as an approach to mitigate the adverse effects of OKT®3 resulting from Fc/FcR engagement (Keymeulen 2005). OKT®3 produces profound, transient T-cell depletion in vivo. It also activates T cells, is strongly mitogenic, and its use in vivo is associated with severe cytokine-release syndrome (incidence >90%). The cytokine-release syndrome (CRS) induced by OKT®3 is characterized by fever, chills, nausea, vomiting and other symptoms, and usually requires corticosteroid therapy to suppress. OKT®3 also is associated with a small incidence of EBV lymphomas (~1%-2%). T-cell activation is strongly facilitated by the interaction of Fc component of OKT®3 with Fc receptors on lymphocytes (Fc/FcR engagement).

Teplizumab is a 150-KD humanized mAb that binds the CD3-e epitope of the T cell receptor (TCR) complex with affinity equal to OKT®3, but it differs from OKT®3 in two properties:

1. The humanization process has resulted in the generation of a mAb that used less than 10% of the original murine amino acids in the antibody construction. The clinical consequence of this property is reduced immunogenicity or formation of anti-idiotypic antibodies.
2. Two amino acids have been changed (leucine234 to an alanine and leucine 235 to an alanine) in the Fc portion of the immunoglobulin that disrupt Fc receptor and complement

component C1q binding. These two amino acid changes were aimed at eliminating the majority of cytokine-mediated toxicity observed during infusions of OKT®3.

The modified Fc component of teplizumab minimizes the activating capacity of the antibody compared with unmodified murine OKT®3.

Teplizumab has been evaluated in a number of clinical trials in the prevention or delay of T1D in high risk individuals and in new onset T1D, as well as in renal and islet allo-transplantation, and psoriatic arthritis. There are ongoing studies evaluating teplizumab in newly-diagnosed pediatric patients (Phase 3 PROTECT study, PRV-031-001) and in combination therapy with a genetically modified strain of Lactobacillus designed to secrete human pro-insulin and human interleukin-10. By far the most extensive clinical trial experience is in children and adults with newly diagnosed T1D, where over 1000 individuals in 7 studies have been treated with teplizumab. Results from these studies suggest that it is a promising candidate for disease modification of T1D. In pilot and proof-of-concept clinical studies conducted in young children, adolescents, and adults, short courses (approximately 2 weeks) of teplizumab treatment have been shown to be safe and well tolerated, resulting in relative sparing of β cell function in those who were recently diagnosed with T1D (Herold 2002, Herold 2005, Herold 2013a, Herold 2013b).

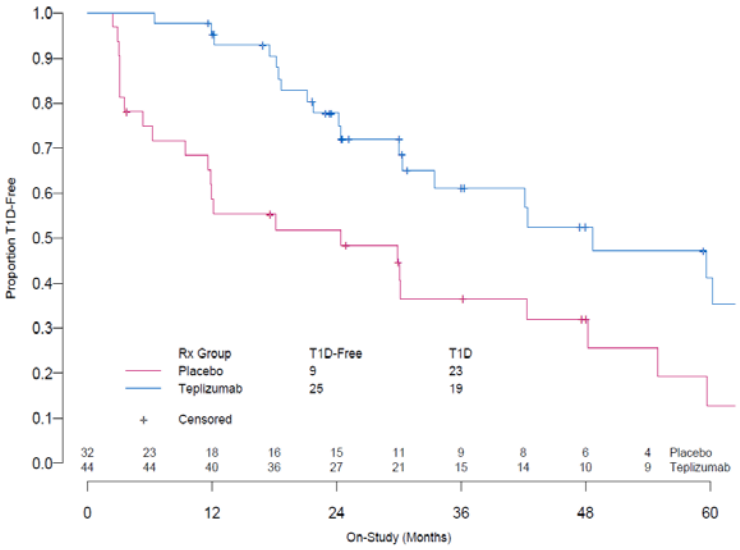
A multi-arm, multinational Phase 2/3 study of teplizumab (known as the "Protégé" study) was previously conducted by MacroGenics and Eli Lilly and Company. Over 500 children and adults 8 to 35 years old with T1D were enrolled within 12 weeks of diagnosis and evaluated in 3 different teplizumab dosing regimens or placebo (Sherry 2011, Hagopian 2013). The study used a novel and untested composite primary endpoint integrating glycemic control, measured by hemoglobin A1c (HbA1c) level, and insulin use; specifically, participants were considered to meet the primary endpoint if they had HbA1c <6.5% and insulin use <0.5 units/kg/day at 1-year post randomization. Although the study did not meet this primary endpoint, the study results in the randomized treatment group (14-day regimen, 9 mg/m^2 dose per course) showed a statistically significant benefit in slowing the decline in C-peptide at 18 and 24 months, which supported the findings of previous studies that teplizumab does have the ability to preserve β cell function in those newly diagnosed with T1D (Hagopian 2013). Furthermore, the effect of teplizumab treatment was even more notable in participants with the following characteristics at the time of study entry: enrolled in sites in the United States, 8 to 17 years of age, higher baseline C peptide levels, and randomized within 6 weeks of TID diagnosis (Hagopian 2013).

2.2.1. Results from the TN-10 Study

The recently completed TN-10 study "Anti-CD3 mAb (teplizumab) for Prevention of Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus" study (referred to as TN-10 hereafter) tested whether a single 14-day course of treatment with teplizumab would delay the time to diagnosis of T1D in relatives of patients with T1D who were at very high risk for the diagnosis based on the criteria of at least 2 autoantibodies and dysglycemia during an oral glucose tolerance test (Herold 2019). Participants were randomized to a single 14-day course of teplizumab or placebo and followed for development of type 1 diabetes using oral glucose tolerance tests performed at 6-month intervals. Seventy-six participants (55/76 [72%] were less than 18 years of age) were randomized (44 to teplizumab; 32 to placebo). Median follow-up was 745 days (range 74-2683 days). The duration of follow up was more than three years in 57 (75%) participants. Type 1 diabetes was diagnosed in 42 (55%) participants.

The primary endpoint was the time to the diagnosis of T1D, which occurred in 19 (43%) teplizumab and 23 (72%) of placebo participants. The hazard ratio of teplizumab to placebo was 0.412 (95% CI: 0.216, 0.783, adjusted Cox proportional hazards, p=0.006) (Figure 1). The annualized rates of diabetes were 14.9% and 35.9% per year, in the teplizumab and placebo arms, respectively.

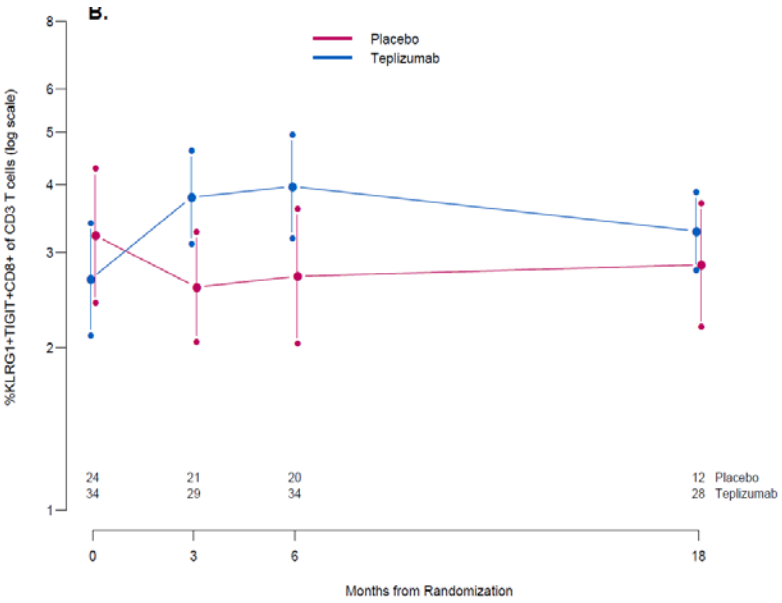
Figure 1: Effects of Teplizumab Treatment on Development of Type 1 Diabetes



Kaplan-Meier estimates of the proportion of participants who had not developed clinical diabetes in the two study arms. The overall hazard ratio was 0.412 (95% CI: 0.216, 0.783) (p=0.006, two-sided, Cox model). The median time to type 1 diabetes was 48.4 months for teplizumab group and 24.4 months for the placebo group. The insert shows the total number of participants with and without clinical type 1 diabetes at the conclusion of the study.

Although the primary mechanism of action of the antibody involves binding the CD3 antigen target on T cells, recent studies have suggested that the mode of action of teplizumab involves induction of CD8+ T cells characterized by the expression of EOMES, TIGIT, and KLRG1. These cells were originally identified by a RNAseq analysis of peripheral blood cells and confirmed by flow cytometry in the clinical responders (Long 2016). In the TN-10 study, an increase in the frequency of the TIGIT+KLRG1+ CD8+ T cells (of the CD3+ cells) in the teplizumab-treated subjects at 3 and 6 months after enrollment was observed compared to baseline and compared to placebo treated participants (Figure 2).

Figure 2: Percentage of KLRG1+TIGIT+CD8+ of total CD3+ T cells in the teplizumab and placebo treated participants.



The mean±95% CI are shown. The estimates and percent increase between the teplizumab vs. placebo groups are (3 months 46.5% (95%CI: 8.23, 98.4%), 6 months 49% (4.13, 113%), 18 months 15.9% (-14.2%, 56.4%). The analysis was performed with log-transformed values by ANCOVA and corrected for the baseline values. The numbers along the X axis indicate the number of samples analyzed.

Studies from other clinical settings suggest that these cells have impaired function (i.e. "exhaustion"). It is postulated that cells with this phenotype are unable to cause the autoimmune killing of insulin producing beta cells that is the hallmark of the disease. These CD8+ T cells are not, however, inactive, since, in the TN-10 study, the few persons with detectable EBV and CMV viral DNA showed rapid resolution (see below). The resolution of EBV and CMV activation and the absence of an increased rate of infectious adverse events suggest that the duration of functional effects of teplizumab on T-cells may be affected by their avidity for autoantigens, viral or other antigens. Subsequent mechanisms involved in the therapeutic effects are incompletely understood.

2.3. Safety Experience with Teplizumab

Much of the safety experience with teplizumab are in Stage 3 T1D individuals. In the Protégé and other clinical studies, teplizumab is generally very well tolerated. In general, there are no major differences in overall adverse events (AEs) of clinical concern and serious adverse events (SAEs) between teplizumab and placebo groups. The most common AEs associated with teplizumab are a decrease in white blood cell counts, nausea and/or vomiting, upper respiratory infections or nasopharyngitis and elevations in AST or ALT and anemia, all usually mild or moderate. The most frequent observation is a decrease in white blood cell count (WBC), including, in order, transient lymphopenia, leukopenia, and neutropenia. Transient lymphopenia has occurred in ~2/3 of teplizumab recipients and is usually mild or moderate, which is consistent with teplizumab's mechanism of action (Sherry 2011, Hagopian 2013). These events are usually self-limited and occur with teplizumab dosing and spontaneously reconstitute. For example, lymphocytes return to 80% of baseline levels within approximately 14 days of dosing. Approximately half of those who receive teplizumab develop a mild rash, sometimes pruritic, during dosing cycles, which spontaneously resolves within 7-14 days. Due to its mechanism of action, cytokine release syndrome is a potential concern with teplizumab dosing but occurs in <10% of teplizumab-treated individuals (for example ~6% in the Protégé study) and is usually mild-to-moderate and well

tolerated. Prophylactic administration of non-steroidal anti-inflammatory drugs (NSAIDs; eg, ibuprofen) and antihistamines (eg, diphenhydramine) appear to reduce the occurrence and the severity of its signs and symptoms significantly.

In the Protégé study, severe AEs were noted in approximately 63% and 30% of teplizumab and placebo participants, respectively (Sherry 2011, Hagopian 2013). The most common (though occurring in less than 10% of teplizumab treated participants) was decreased white blood cell counts. Three deaths occurred and were evaluated by the principal investigator in accordance with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) guidelines. The specific causes of deaths and relationship with teplizumab are listed as: (1) "unknown" for which the relationship was listed as "none"; (2) "anterior myocardial infarction with ventricular tachycardia and cardio-respiratory arrest" for which the relationship was listed as "not related"; and (3) "diabetic ketoacidosis" for which the relationship was listed as "unlikely".

Despite the decrease in WBC, overall infections were not increased following teplizumab treatment. However, in the Protégé study there were 10 cases of herpes zoster (the result of reactivation of varicella zoster virus [VZV], the causative agent of chicken pox and shingles) in teplizumab-treated patients; all cases resolved without consequence. In the study, other herpes virus infections (eg, cytomegalovirus and Epstein-Barr virus) were not increased with teplizumab treatment (Sherry 2011, Hagopian 2013).

More information is available in the Investigator's Brochure (IB).

In the recently completed TN-10 study, the adverse events in those with Stage 2 disease are shown below.

Grade of adverse events in the TN-10 trial designated as possibly, probably, or definitely related to study drug are shown in Table 1 and adverse events by category related to study drug are shown in Table 2.

Table 1: Grade of adverse events related to study drug

Severity (Grade)	Treatment Group	
	Anti-CD3 MAB No. (%)	Placebo No. (%)
0/1	1 (2.3)	10 (31.2)
2	23 (52.3)	20 (62.5)
3	20 (45.5)	2 (6.2)
4	0 (0)	0 (0.0)
5	0 (0)	0 (0)
Total	44 (100.0)	32 (100.0)

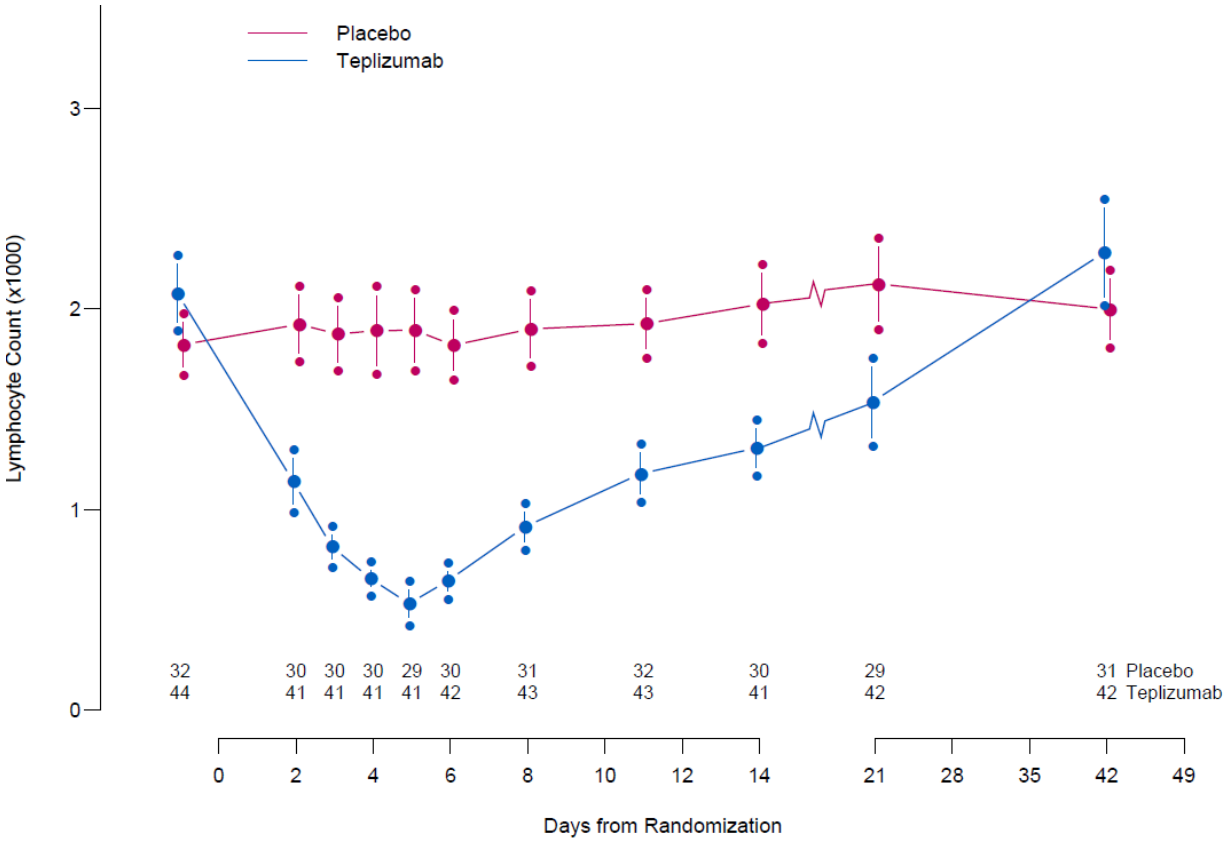
Table 2: Adverse events by category and designated and possibly, probably, or definitely related to study drug.

Adverse Effect Category	Teplizumab		Placebo	
	No. of Events#	No. of Participants (%)	No. of Events	No. of Participants (%)
Blood/Bone Marrow***	45	33 (75)	2	2 (6.2)
Dermatology/Skin***	17	16 (36.4)	1	1 (3.1)
Pain	11	5 (11.4)	5	3 (9.4)
Infection	8	5 (11.4)	5	3 (9.4)
Gastrointestinal	5	4 (9.1)	3	3 (9.4)
Metabolic/Laboratory	7	4 (9.1)	2	2 (6.2)
Pulmonary/Upper Respiratory	6	4 (9.1)	0	0 (0)
Constitutional Symptoms	3	2 (4.5)	0	0 (0)
Allergy/Immunology	2	2 (4.5)	0	0 (0)
Cardiac General	1	1 (2.3)	1	1 (3.1)
Endocrine	0	0 (0)	2	2 (6.2)
Vascular	1	1 (2.3)	1	1 (3.1)
Neurology	1	1 (2.3)	0	0 (0)
Ocular/Visual	1	1 (2.3)	0	0 (0)
Musculoskeletal/Soft Tissue	2	1 (2.3)	0	0 (0)
Hepatobiliary/Pancreas	0	0 (0)	1	1 (3.1)
Syndromes	1	1 (2.3)	0	0 (0)
Hemorrhage/Bleeding	1	1 (2.3)	0	0 (0)
Total Events and Individuals	112	44 (100)	23	32 (100)

One individual who was treated with teplizumab, was diagnosed with serum sickness and received an abbreviated course of prednisone. This adverse event is captured under “pain” (of joints) above.

Similar to previous studies with teplizumab in new onset type 1 diabetes patients, the lymphocyte count declined to a nadir on day 5 by 72.3% (interquartile range: 82.1, 68.4%) ($p<0.0001$) (Figure 3). Fifteen (34.1%) of the grade 3 events in the teplizumab group involved lymphopenia during the first 30 days after study drug administration. The lymphocyte counts recovered quickly: Lymphopenia resolved in all participants by day 45 except in 1, whose counts returned on day 105.

Figure 3: Absolute lymphocyte counts in the study groups are shown over the first 7 weeks after enrollment



A spontaneously resolving rash, as previously noted, occurred in 36% of teplizumab-treated participants. The rates of infection were similar in the two treatment arms.

Anti-CD3 mAb treatment has been associated with Epstein-Barr virus (EBV) reactivation (Herold 2003, Mach 1992). At entry, 30 participants (39%) (16 teplizumab and 14 placebo) had antibodies against EBV. At weeks 3-6 after study drug treatment, there was quantifiable EBV DNA in whole blood in 8 of the seropositive participants – all in the teplizumab group, one of whom had symptoms of pharyngitis, rhinorrhea, and cough on day 38. In these participants, the EBV DNA levels were below the level of quantification between day 43 and 134 (average 77 days). At entry, 17 participants (10 teplizumab and 7 placebo) had antibodies against cytomegalovirus (CMV). One teplizumab participant, who was CMV seropositive, had detectable levels of CMV DNA at day 20 that was undetectable by day 42.

2.4. Use of Teplizumab in Children

The majority of new cases of T1D occur in children under the age of 18. Moreover, given that the duration of diabetes is a significant risk factor for the development of diabetic complications and the clearly recognized difficulty in attaining excellent metabolic control of diabetes during adolescence. Diagnosis of T1D before the age of 20 incurs greater morbidity and loss of life years than when the diagnosis is made in adulthood. In the TN-10 trial, 72% of the participants were

children. The adverse event experience was not significantly different in adults and children. Altogether, more than 470 children have received teplizumab in clinical trials.

The study procedures, while greater than minimal risk, offers the possibility of benefit due to the close monitoring for all participants and the delay in diagnosis of T1D. Assent of children along with consent of their guardians will be obtained, as appropriate, prior to any study procedures.

Please refer to the Teplizumab IB for further non-clinical and clinical information on the antibody.

2.5. Benefit/Risk Assessment

Type 1 diabetes (T1D) is an autoimmune disease that results in a severe metabolic disease of glucose dysregulation. T1D is associated with significant short- and long-term complications and early death. Even with the best metabolic control using the most current insulins and glycemic monitoring devices, these risks are not eliminated. There is an urgent need to develop a disease modifying therapy for T1D.

Clinical studies with teplizumab in T1D have shown that it is effective in preserving beta cell function (as measured by C-peptide) and hence endogenous insulin production (Herold 2019). In the previous Protégé Study, teplizumab resulted in a statistically significant preservation of C-peptide, compared to placebo, at 2 years. As described in natural history studies, preservation of residual beta cell function (as measured by C-peptide levels) is protective against short-(hypoglycemic episodes) and long-term complications of T1D, including retinopathy, nephropathy and other cardiovascular events (Steffes 2003, Sorensen 2013, Lachin 2014, Kuhtreuber 2015).

The main risks of teplizumab consist of transient lymphopenia and transient self-limited (mild to moderate) rash. Cytokine release syndrome is infrequent (~6%) and there is no overall increased risk of clinical infection or cancers.

Given the potential for important benefit in short- and long-term T1D outcomes compared to the transient, mild to moderate risks of teplizumab, the prospect of benefit outweighs the risk of participating in this study.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of teplizumab may be found in the IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of teplizumab treatment, administered intravenously (IV) to participants in the TN-10 trial who have developed T1D.	• Incidence of treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs)
Secondary	
• To evaluate the pharmacokinetics (PK) and immunogenicity of teplizumab • To evaluate whether teplizumab treatment reduces the loss of β cells, over 78 weeks (18 months), in individuals with recent diagnosis of T1D. • To evaluate key clinical parameters of diabetes management, including insulin use, hemoglobin A1c (HbA1c), and clinically important hypoglycemic episodes over 78 weeks • To evaluate whether treatment with teplizumab increases the frequency of exhausted T cells	• Levels of teplizumab in the serum and anti-drug antibodies • The area under the time-versus-concentration curve (AUC) of C-peptide after a 4-hour (4h) mixed meal tolerance test (MMTT), a measure of endogenous insulin production and β cell function, over 78 weeks • HbA1c levels; insulin use, defined as a daily average in units per kilogram per day (U/kg/day); and frequency of clinically important hypoglycemic episodes over 78 weeks • Frequency of CD8+ TIGIT+ KLRG1+ T cells

4. Study Design

4.1. Overall Design

The is a single-arm, multicenter, open-label clinical trial.

Teplizumab-treated and placebo participants in the TN-10 trial who develop clinical type 1 diabetes after the conclusion of that trial, are eligible to enroll and receive teplizumab treatment in this open-label study within one year of clinical T1D diagnosis.

Number of Participants:
Up to 30 participants may be enrolled in this study.

Treatment and Study Duration:
All participants will receive a 12-day course of teplizumab given through daily IV infusion. Participants will have a screening period of up to 4 weeks, a treatment period of 12 days, and a follow-up period of up to 78 weeks (18 months) from the first dose of treatment.

4.2. Scientific Rationale for Study Design

It is recognized that participants eligible for this study have undergone further decline in beta cell mass and function since their participation in the TN-10 trial, leading to the need for exogenous insulin replacement in order to maintain glycemic control. At this juncture, it is critical to preserve the remaining beta cell function as this leads to better short-term (ie, hypoglycemic episodes) and long-term outcomes including retinopathy, nephropathy and other cardiovascular events (Steffes 2003, Sorensen 2013, Lachin 2014, Kuhtreuber 2015). Phase 2 and Phase 3 clinical trials with teplizumab have consistently shown significant preservation of beta cell function as measured by C-peptide in patients with newly diagnosed T1D (Hagopian 2013; Herold 2013a; Herold 2013b; Herold 2019). Therefore, it is anticipated that the benefit of teplizumab treatment on preservation of beta cell function may be realized in previous participants of the TN-10 study who now have developed clinical type 1 diabetes.

Between 20% and 56% of teplizumab treated patients develop anti-drug antibodies that may be neutralizing antibodies (NAb). These antibodies can be detected within 2 weeks after the drug has been given. They may affect the immunologic effects of additional courses of teplizumab treatment, but a safety concern has not been identified – second courses of teplizumab did not have an increased frequency of adverse events compared to the first course. In this study, the responses to teplizumab treatment in participants with and without anti-drug antibodies will be analyzed. The time interval between the first (under the TN-10 protocol) and second course of teplizumab treatment in this study (PRV-031-002) is longer than has previously been tested and therefore, the effect of anti-drug antibodies is not known. Thus, these study participants are different from those who previously have received two courses of teplizumab. As eligible and consenting placebo participants in the TN-10 trial will also be treated with teplizumab upon the diagnosis of clinical T1D, the immunologic effects of teplizumab in the placebo group, who will receive teplizumab for the first time, will serve as a comparator to individuals previously treated with teplizumab.

4.3. Justification for Dose

In previous clinical studies of teplizumab in T1D, a number of dosing regimens have been evaluated that have included children and/or adults. These studies have evaluated single multi-day courses of teplizumab and 2 multi-day courses either 6 or 12 months apart. Although the goals, stage of T1D, and entry criteria differed between these studies, all have shown that teplizumab was well tolerated with an acceptable safety profile, and an ability to preserve β cell function and improve clinical outcomes in study populations or specific sub-populations. It is these effects that support further evaluation and clinical development of teplizumab as a first-in-class therapy for children and adolescents newly diagnosed with T1D (Herold 2002, Sherry 2011, Hagopian 2013, Herold 2005, Herold 2013a, Herold 2013b).

Of note, the 14-day regimen evaluated in Protégé (and other previous studies including the TN-10 The most extensive and detailed evaluation of teplizumab in T1D is from the Phase 2/3 "Protégé" study in which 2 multi-day courses of teplizumab were given 6 months apart in children and adults 8 to 35 years old who were diagnosed with T1D within 12 weeks of T1D diagnosis. In that study, three dosing regimens of teplizumab were evaluated and included: (1) a 14-day course with a cumulative dose of 9.0 mg/ m^2; (2) a 14-day course with a cumulative dose of 3.0 mg/ m^2; and (3) a 6-day course with a cumulative dose of 2.4 mg/ m^2. In the open-label Phase 2 segment of Protégé, participants received the 14-day regimen of 9.0 mg/m2/course at enrollment and 26 weeks later to assess safety and tolerability before the double-blind study was started. The Phase 3 segment studied the three teplizumab dosing regimens in comparison to placebo. The open label Phase 2 segment of Protégé enrolled 38 participants, and the randomized, double-blind Phase 3 segment enrolled 207, 102, and 106 teplizumab-treated participants, respectively, and the placebo arm 98 participants (Sherry 2011, Hagopian 2013).

In addition to assessments of safety and efficacy, the Protégé study conducted extensive PK and immunogenicity evaluations. From this data, a detailed population PK model has been developed using a two-compartment (peripheral and central) model with saturable binding kinetics incorporating body surface area (BSA), proportional dosing, and teplizumab AUC, trough concentration, and peak concentration. These findings showed that PK was independent of age, gender, race, region, disease state or onset, although it was influenced by antidrug-antibody response.

As described earlier, although the previously untested and unevaluated composite primary endpoint was not met in the entire study population of Protégé, a positive effect of teplizumab in T1D was confirmed in Protégé subpopulations, supporting findings from a number of previous clinical studies. Specifically, participants from certain regions (eg, the United States) who were 8-17 years old, who had teplizumab initiated within 6 weeks of T1D diagnosis and with higher C-peptide levels at study entry showed significant retention of endogenous insulin production through 2 years compared to placebo treated participants.

A 14-day course necessitates participants and their parents or guardians (required by pediatric participants) to be available every day for 2 entire consecutive weeks and associated weekends. This requirement is seen to be particularly challenging to children and adolescents and their families due to work and school obligations and therefore may have a negative influence on recruitment and retention as well as a significant bias in a pivotal study.

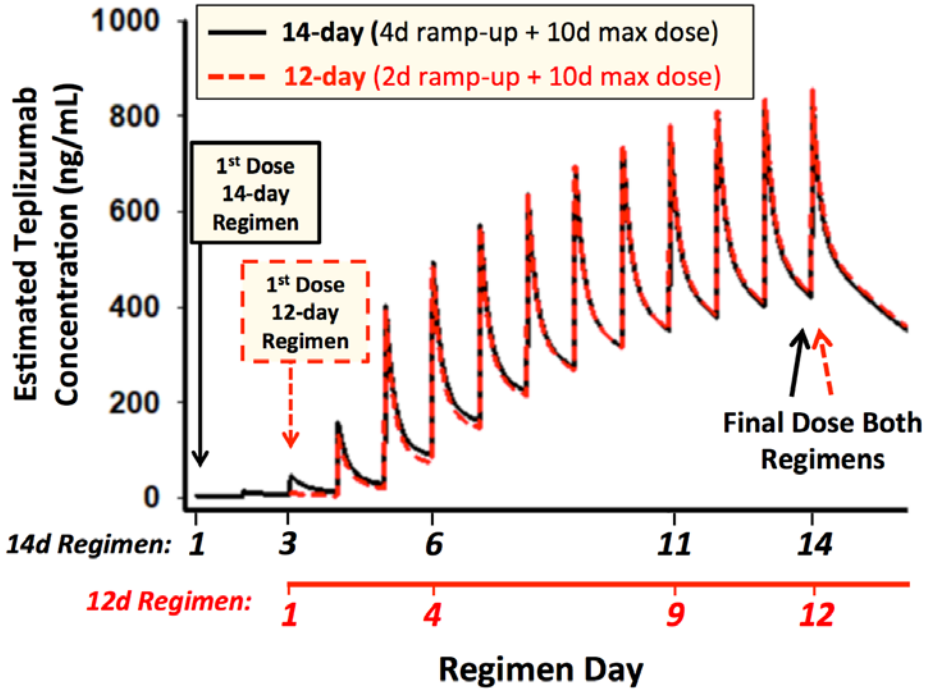
With the realization of the potential negative impact on many aspects of the clinical trial of a 14-day treatment course combined with the significant experience with teplizumab, in this study we propose to use a regimen that is more acceptable to participants and their families that delivers clinically overlapping exposures that could support approval for teplizumab.

We propose to modify the dosing regimen to 12 days: Day 1: 106 µg/m^2, Day 2: 425 µg/ m^2, and Days 3-12: 850 µg/ m^2/day. During the first 2 days of ramp-up, approximately 5.9% of the total dose is given. In the last 10 days, ~94% of the total dose is delivered in equally divided doses.

Compared to a 14-day dosing regimen, this study's 12-day teplizumab course has a modified 2-day ramp-up phase but also has a 10-day fixed-, maximal dosing period like the 14-day course. Based on calculations, the amount of teplizumab given in the 12- and 14-day approach only differs by 0.005 mg/m^2. But due to practical aspects of rounding and calculating the BSA and a given dose, these courses are considered clinically equivalent.

As shown in the PK simulations in Figure 4, the first 2 doses in the 14-day regimen are calculated to have very low, almost negligible, serum concentrations with serum concentrations of the last 11 doses of both regimens that are superimposable. In both instances, >90% of the total dose per course is given in the final 10 days in similar equally divided doses (0.850 mg/m^2 in the 12-day course versus 0.826 mg/m^2 in the 14-day course). The first 2 days of the 14-day course delivers a nominal amount (ie <2.0%) of the course's total dose. The final trough concentrations (426±220 ng/mL [14-day regimen] and 435±225 ng/mL [12-day regimen]), as well as the elimination times are overlapping in both regimens.

Figure 4: PK Simulation of 12-Day and 14-Day Dosing Regimens



Taken together, this study will evaluate a more participant and family-friendly approach to deliver the same dose of 9.0 mg/m^2 of teplizumab over a course of 12 days, which has been shown to be

well tolerated, safe and effective in preserving β cell function. Because of the similarities and overlap of the regimens and exposures, data from this study can be combined with data from other studies to support the application and approval for teplizumab as a disease modifying therapy for the study population in those recently diagnosed with T1D.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit shown in the Schedule of Events (Section 1.3).

The end of the study is defined as the date of the last visit of the last participant in the study.

5. Study Population

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria are met:

1. Previous participant in the TN-10 study.
2. Participant has received a diagnosis of T1D after the conclusion of the TN-10 study, according to the criteria from the American Diabetes Association (ADA).
3. Participant is able to initiate teplizumab treatment required in this study within 1 year of T1D diagnosis.
4. If participant is female with reproductive potential, she must have a negative pregnancy test prior to enrollment and be willing to avoid pregnancy for at least 18 months from the first dose of study drug.
5. Participant is willing and medically able to postpone live vaccine immunizations for 1 year after receiving the last dose of study drug in this study.
6. Participant is willing to forego other forms of experimental treatment during the entire study.
7. Participant and/or guardian has given informed consent and assent as applicable.

5.2. Exclusion Criteria

Participants will be excluded from the study if any of the following criteria is met at screening or before the first dose is given:

1. Lymphopenia (< 1000 lymphocytes/μL)
2. Neutropenia (< 1500 polymorphonuclear cells [PMNs]/μL)
3. Thrombocytopenia (< 150,000 platelets/μL)
4. Anemia (hemoglobin < 10 g/dL)
5. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1.5 x upper limit of normal (ULN)
6. Total bilirubin >1.5 x ULN. Exception: participants with the diagnosis of Gilbert's syndrome may be eligible if they have no other causes leading to hyperbilirubinemia.
7. Chronic active infection except localized skin infections. This may be discussed with the Medical Monitor on a case by case basis.
8. Participant has any of the following regarding tuberculosis (TB):
    - A history of latent or active TB
    - Signs and/or symptoms of TB
    - Recent close contact with a person with known or suspected active TB, unless appropriate isoniazid prophylaxis for tuberculosis was given
    - A history of a chest X-ray consistent with active TB or old, inactive TB,
    - A history of a positive purified protein derivative (PPD) skin test result (>10 mm induration)
    - At screening is positive or repeatedly indeterminate with an approved interferon-gamma release assay (IGRA; eg, QuantiFERON-TB test) or PPD.

- If required by local, regional or national regulations, a recent (within 3 months) chest X-ray or one conducted at screening read by a qualified radiologist consistent with current, active TB or old, inactive TB

9. Vaccination with a live virus within 8 weeks before first dose of the study drug
10. Vaccination with a killed virus within 4 weeks before first dose of the study drug
11. A history of infectious mononucleosis within the 3 months before screening.
12. Laboratory or clinical evidence of acute infection with EBV or CMV.
13. Serological evidence of current or past human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
14. Currently pregnant or lactating or planned pregnancy within 18 months 2 years after receiving the last dose of the study drug
15. Chronic use of steroids or other immunosuppressive agents.
16. A history of asthma or atopic disease requiring chronic corticosteroid treatment.
17. Untreated hypothyroidism or active Graves' disease.
18. Current use of non-insulin pharmaceuticals or dietary supplements that may affect glycemic control.
19. Participation in any therapeutic drug or vaccine clinical trial within 12 weeks before the first dose of study drug.
20. Any condition that, in the opinion of the investigator, would interfere with the study conduct or the safety of the participant.

5.3. Enrollment

Potential study participants will be identified through previous participation in the TN-10 trial. TN-10 participants, regardless of whether they received teplizumab or placebo in that study, are invited and screened for this study if they have been diagnosed with T1D and can receive teplizumab within 12 months of the diagnosis.

6. Study Drug Dosing

6.1. Study Drug Administered

All participants will receive an IV infusion of teplizumab once daily for 12 consecutive days.

The participant's body surface area (BSA) will be calculated by the study pharmacist using the Mosteller formula. The BSA will be calculated on Study Day 1 and will be based on the participant's height and weight on that day. This calculation will be used for the doses given over the entire 12-day treatment course. For dosing purposes, the participant's BSA should be rounded up to the nearest tenth place regardless of the number in the hundredth position. For example, if the BSA is 1.61 m^2, it will be rounded up to 1.7 m^2; if the BSA is 1.67 m^2, it will also be rounded up to 1.7 m^2. The dose should be rounded to the nearest whole number.

The drug dosing is:

Day 1: 106 µg/m^2

Day 2: 425 µg/m^2

Days 3-12: 850 µg/m^2 daily

Total per course: 9.0 mg/m^2

The Mosteller formula is as follows:

BSA (m^2) = ([Height(cm) x Weight(kg)]/ 3600)^{½}

Teplizumab is administered via an IV infusion over a minimum of 30 minutes in the research or hospital setting. The daily time of the infusion should be consistent but may be adjusted by a time window of ±4 hours on each day. If there are signs or symptoms of infusion reaction during the 60-minute observation period, the participant should be observed for an addition al 60 minutes or until the reaction resolves, whichever is longer.

6.2. Preparation/Handling/Storage/Accountability

The formulation of teplizumab consists of 10 mM sodium phosphate, 150 mM sodium chloride, and 0.05 mg/mL Tween 80, with pH 6.1.

Final drug product will be provided at a concentration of 1 mg/mL for a total of 2 mg of recoverable drug product per vial.

The vials should be stored upright at 2°–8°C and must not be frozen or shaken. Because there is no preservative and drug loss occur over time, administration of the study drug should begin as soon as possible and no later than 2 hours after preparation. The drug may be prepared into a bag for infusion and delivered by gravity or by infusion pump. Intravenous drug delivery devices, including IV bags and tubing, must be composed of polyvinyl chloride (PVC). Refer to Pharmacy manual for details.

Laboratory studies that will be obtained prior to each dose are described in the Schedule of Events (Section 1.3) and Appendix 2 (Section 10.2). The same-day results of chemistries (including liver function tests [LFTs]), WBC counts, hemoglobin, hematocrits and platelets must be reviewed prior to commencement of the drug infusion on each dosing day.

6.3. Concomitant Therapy

6.3.1. Diabetes Management and Insulin Use

All participants should receive intensive diabetes management of their T1D using approved therapies according to the recommendations of ADA to achieve glucose levels that appear to decrease some of the short-term and long-term sequelae of T1D. Currently the glycemic targets by the ADA are focused at management strategies to achieve an HbA1c level of <7.5% (58 mmol/mol) for individuals 17 years old and younger and <7.0% (53 mmol/mol) for those 18 years and older, while minimizing severe or frequent hypoglycemic events. If there are local, regional, or national recommendations to be followed that supersede ADA recommendations, these glycemic control targets (ie, HbA1c or glucose levels) should not be more liberal (ie, higher) than the ADA recommendations. The Investigator will document, in the case report form (CRF) and/or the source documents, the glycemic goals and the guidelines being followed.

The glycemic goal should be attempted through proper glycemic monitoring, administration of exogenous insulin, and monitoring of activity level and diet. Exogenous insulin may include rapid, intermediate, and/or long-acting insulins, administered intermittently or via the use of a personal insulin pump. Blood glucose levels should be measured at least 4 times a day, including before meals and before bedtime. Approaches to achieve these HbA1c goals will be the responsibility of the participant, their caregivers, and their healthcare providers.

Insulin use, including the type of products, dosages, and dosing schedules, is expected to change during the course of the study. As part of routine T1D clinical care, if the caring physician judges it to be clinically appropriate, a participant's insulin dose may be increased, reduced, or even discontinued.

Insulin Discontinuation

If a participant has achieved a HbA1c level of ≤6.5% with insulin use of ≤0.25 U/kg/day, insulin therapy can be discontinued. The participant's blood glucose and HbA1c levels should continue to be monitored per protocol, and urine ketones should be tested at home once a day. During routine blood glucose monitoring, if the participant's blood glucose level exceeds 200 mg/dL and/or urine ketone level is moderate or greater, the participant should consult with their primary physician and/or the clinical site staff for further evaluation. If the fasting blood glucose exceeds 126 mg/dL or HbA1c exceeds 6.5%, as documented by repeat testing, the resumption of insulin therapy should be considered.

6.3.2. Prophylactic Medications

Ibuprofen and antihistamine will be administered prophylactically prior to teplizumab infusion on the first 5 days of treatment. After Day 5, the use of pre-medication is optional. If ibuprofen is contraindicated, acetaminophen should be given instead. Further dosing of ibuprofen, antihistamines, and/or acetaminophen can be used as needed for fever, malaise, headache, arthralgia, or rash. All prophylactic medications administered should be recorded on the concomitant medication CRF.

6.3.3. Prohibited Medications

Participants will be instructed not to use steroids, (eg, prednisone [topical or systemic]), other immunosuppressive agents, or chronic inhaled or nasal corticosteroids during this trial in order to reduce infectious risks and to prevent possible impact on diabetes outcome. A short course (ie, approximately 2 weeks or less) of systemic (including oral, inhaled or parenteral) corticosteroids may be used for treatment of a transient condition. In the event of a medical condition requiring glucocorticoid treatment, they may be used after discussion with the Medical Monitor. However, no individual will be withdrawn from analysis if this occurs.

Participants will be instructed not to receive live vaccinations for 1 year after dosing. In addition, participants should not receive vaccination with a killed virus vaccine within 8 weeks after the last dose of the study drug, unless this is approved by the Medical Monitor.

6.3.4. Emergency Precautions

Before every infusion of study drug, appropriate emergency equipment and trained personnel should be present. At a minimum, the following will be available:

- Epinephrine 1 mg doses (or resuscitation dose recommended by local, regional or national authorities) for IV injection
- Dexamethasone 10 mg (or equivalent glucocorticoid) for IV injection
- Diphenhydramine: 50 mg (or equivalent antihistamine) for IV injection
- Resuscitation equipment and other supplies for the emergency management of an allergic/toxic reaction.

If AEs develop during infusion, the infusion may be slowed or interrupted, as determined by the Investigator. If interrupted, the infusion may be restarted, preferably at a slower rate, if deemed reasonable by the Investigator. Any changes in the infusion rate must be recorded with the reason for the change. In any cases of AEs determined or suspected to be related to the infusion of the study drug, the participant should be treated using appropriate medical practices and procedures.

During or after the infusion of study drug, if a participant experiences any of the following signs, the participant will be observed, and the severity of the reaction will be evaluated:

- Fever of >38.5°C (101.3°F)
- Rigors or myalgias
- Pain, swelling, or edema near the infusion site
- Local or systemic rash
- Mucosal congestion or edema
- Significant (eg, 30%) drop in systolic or diastolic blood pressure or increase in resting heart rate
- Hyperventilation, wheezing or difficulty breathing

- Change in mental status

Acetaminophen (or similar drug) and/or additional NSAID may be given if needed, glucocorticoid treatment may be considered. The participant should be treated using appropriate medical practices and procedures. The participant will be continuously monitored until their clinical status returns to baseline or is significantly improved.

If an infusion is discontinued, an estimate on the volume of the infusion given and a quantitative assessment of the remaining volume should be documented.

The Medical Monitor should be notified of all cases of actual or suspected infusion reactions and AEs thought to be related to the study drug infusion.

7. Interruption or Discontinuation of Study Drug Treatment and Participant Discontinuation/Withdrawal

A participant will not be automatically withdrawn from the study if they temporarily or permanently discontinue study drug before the end of the treatment course. If a participant permanently discontinues study drug for any reason, they should be encouraged to return for the Early Termination visit.

Unless lost to follow-up, SAEs must be reported for participants who withdraw early from the study for one year after their last study drug dose (Section 8.4.1).

7.1. Interruption of Study Drug Treatment

Blood samples will be drawn for clinical laboratory tests, as listed in Section 1.3, and the results will be reviewed by the Investigator before the study drug can be administered on each day of the treatment.

Study drug dosing may be interrupted temporarily, for an individual participant, if any of the following medically important events occur:

- A significant infection, defined as:
  - Any severe infection meeting SAE criteria (Section 10.3.2), or
  - Any clinically significant infection not meeting SAE criteria but per Investigator's judgment might put the participant at risk, or
- An SAE, a study drug-related severe AE, or an AE that puts a participant at risk, defined as:
  - Any SAE or
  - Any severe AE that is considered related (possibly, probably, or very likely related) to study drug (as defined in Section 10.3.1), including but not limited to an infusion reaction categorized as a severe or SAE by the Investigator.
  - Any AE (including mild or moderate) of any relatedness to study drug that leads to the Investigator to believe that further dosing of study drug during that course puts the participant at undue risk.
- If any of the following out-of-range lab results is observed (normal range per local lab reference ranges), the test may be repeated on the same day. If the repeated test result normalizes, that day's dose may be given. If the value is still in the indicated range or worsens, or if the test cannot be repeated on the same day, that day's dose should be withheld.
  - ALT and/or AST >3 x ULN but ≤5 x ULN
  - Total bilirubin >2 x ULN but ≤3 x ULN
  - Platelet count >50,000 but ≤100,000
  - Hemoglobin >8.5 g/dL but ≤10 g/dL

Note: When clinical and laboratory abnormalities are considered related to T1D disease activity (ie, hypoglycemia and hyperglycemia) and study drug is not considered a contributing factor, administration may not need to be modified. The site Investigator should consult with the Sponsor if this is encountered.

If the above events resolve within 2 days, study drug dosing may be resumed according to the original schedule. The treatment course will not be extended beyond 12 days.

If the above events do not resolve after 2 consecutive days of interruption, the Medical Monitor must be consulted regarding continuation of study drug dosing.

7.2. Discontinuation of Study Drug Treatment

The study drug should be discontinued permanently if any of the following events occur:

- The Investigator believes that for safety or tolerability reasons it is in the best interest of the participant to discontinue study drug.
- A female participant becomes pregnant. Note: The "Pregnancy Report Form" should be submitted for all pregnancies that occur in a study participant. Pregnancy should be followed for outcome and any premature terminations reported. The health status of the mother and child including date of delivery and the child's sex and weight should be reported after delivery.
- A severe infection requiring inpatient hospitalization or repeated doses of parenteral antibiotics
- A severe hypersensitivity reaction, such as anaphylaxis or angioedema with or without requiring hemodynamic support (ie, epinephrine and/or blood pressure medications) or mechanical ventilation, to the study drug or an infusion reaction (including cytokine release syndrome) with signs or symptoms categorized as an SAE.
- The participant has a clinically significant cardiovascular event.
- The participant is diagnosed with a malignancy, lymphoma or a lymphoproliferative disorder.
- If any of the following lab values is observed (normal range per local lab standard), the next study drug dose should be held until a repeat test is obtained and evaluated. If the out-of-range result is confirmed on two consecutive dosing days, the participant should be discontinued from any further study drug treatment.
  - ALT and/or AST >5X ULN
  - Total Bilirubin >3X ULN
  - ALT and/or AST >3X ULN **AND** Total Bilirubin >2X ULN (Hy's Law criteria)
  - Platelet count <50,000/µL
  - Neutrophil count <500 cells/µL
  - Hemoglobin of <8.5 g/dL

- Any ≥Grade 3 AE during dosing other than:
  - Lymphopenia
  - Neutropenia
  - Low total WBC
  - Hypoglycemia or symptoms and signs of a hypoglycemic episode
  - Hyperglycemia or symptoms and signs related to hyperglycemia
  - Fatigue or malaise
  - Insomnia
  - Cheilitis
  - Dry skin
  - Nail changes
  - Hot flushes or flashes
  - Headache
  - Myalgia
  - Flu-like syndrome
- Any medically important event such as a concurrent illness, complications, or abnormal laboratory result that, in the opinion of the Investigator, contraindicates continued dosing of the participant
- Administration of prohibited medication or dose modification of concomitant medications that necessitate discontinuation of study drug administration
- A general lack of compliance with study visits and procedures per study team or a missing 3 consecutive study drug administrations

The Study Medical Monitor must be notified within 24 hours of any participant who is permanently discontinued from study drug dosing. Participants who have study drug dosing permanently discontinued will be encouraged to receive follow-up care and evaluation as scheduled, unless consent for follow-up is withdrawn.

7.3. Participant Discontinuation/Withdrawal from the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent/assent
- Death
- Study Investigator or Sponsor, for any reason, decides the participant should be withdrawn from the study.
- Pregnancy (see Section 8.4.5)

When a participant withdraws before completing the study, the Sponsor is to be notified and the reason for withdrawal is to be documented.

If a participant withdraws from the study before the end of study, all attempts should be made to obtain Early Termination assessments.

7.4. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

If a participant is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the participant and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

8. Study Assessments and Procedures

The assessments and procedures required in this study are listed in the Schedule of Events table in Section 1.3.

It is recognized that the amount of blood that may be drawn for research purposes in children and adults may not exceed certain limits, both at a single visit and over a set time period. In any participant whose clinical condition might be adversely affected by removal of the blood volumes stated in this protocol, for example, a participant with significant anemia or compromised cardiac output, Investigators should consider further limiting the volume of blood withdrawn for research purposes. In instances of medical need, it is the responsibility of the Investigator and/or participant's healthcare providers to determine if blood draws in excess of the protocol-stated volumes should occur. Because blood sampling in excess of those mandated by the protocol may be taken in the course of providing care during this study, sites must ensure that all instances of blood collection in excess of permitted volumes are recorded and justified in the participant's record.

Additional blood volumes may be collected by individual sites and will be included in the site-specific informed consent form.

8.1. Screening and Baseline Assessments

8.1.1. Screening (Visit -1)

This study will enroll former participants of the TN-10 protocol who have developed T1D within the past 12 months.

The participant/parent/guardian will be asked to sign an informed consent and/or assent describing the purpose, risks, and benefits of screening for the trial. A participant/parent/guardian's signature indicates that he/she understands the potential risks and benefits of study participation. During the screening visit, clinical tests will be performed to determine eligibility, as described in the Schedule of Events (Section 1.3).

Any participant either not eligible or not willing to be enrolled into this study is eligible for continued follow-up as part of the Long-Term Investigative Follow-Up in TrialNet Study (LIFT, TN-16).

8.1.2. Baseline Assessments and Initiation of Teplizumab Treatment (Visit 1)

Participants will undergo a 4-hour mixed meal tolerance test (4h MMTT) and other baseline clinical tests at Visit 1, as indicated in the Schedule of Events (Section 1.3). All relevant laboratory and clinical data will be reviewed to confirm eligibility and document baseline values. Subsequently, eligible participants will receive the first dose of teplizumab IV infusion at the same visit.

8.2. Post-Baseline Visits

Participants will complete a 12-day course of teplizumab treatment and return to the study site for follow-up assessments through Week 78, as outlined in the Schedule of Events (Section 1.3).

Participants who discontinue the study before the final visit at Week 78 should undergo the assessments listed for the Early Termination (ET) visit.

8.3. Efficacy Assessments

During the study period, all participants will be closely monitored for T1D control, insulin use, AEs and laboratory abnormalities, undergo 4-hour MMTT every 6 months, and provide blood samples for analyses.

8.3.1. Metabolic Assessments

A 4h-MMTT will be performed at study entry (Visit 1) and every 6 months. At each study visit, the amount of exogenous insulin that is being taken over the 3 days prior to the visit will be documented. HbA1c levels will be measured prior to study drug administration and at each of the designated study visits.

8.3.1.1. Hypoglycemia

Instances of significant impairment consistent with hypoglycemia and requiring assistance (ie, often referred to as "severe" hypoglycemia), even in the absence of a blood glucose reading, are classified as "Level 3 Hypoglycemia" (IHSG 2017). Level 3 hypoglycemia may include cognitive impartment, altered/loss of consciousness, confusion, seizure, syncope/fainting, or coma, and support may be general assistance, glucagon, or oral carbohydrate (ie, fruit juice or glucose tablets). Such episodes may or may not require medical attention or hospitalization.

This study will consider clinically significant hypoglycemia to be Level 3 or greater hypoglycemia as defined below.

For AE reporting purpose, the severity of a hypoglycemia event should be identified by the Investigator and classified according to CTCAE v5.0 as follows:

- Grade 3 hypoglycemia: 30-39 mg/dL (1.7–2.1 mmol/L). This is considered severe or medically significant but not immediately life-threatening. Hospitalization or prolongation of hospitalization is likely indicated. It is considered disabling and limits self-care.
- Grade 4 hypoglycemia: ≤29 mg/dL (1.6 mmol/L). This is considered life threatening (eg, seizures) with urgent intervention indicated.
- Grade 5 hypoglycemia: Hypoglycemia resulting in death.

8.3.2. Mechanistic Outcome Assessments

Immune and gene-expression tests to further understand mechanisms that may be underlying the T1D disease process and response to therapy will be conducted. For this purpose, plasma and serum samples for the analyses of peripheral blood mononuclear cells (PBMCs), DNA, RNA, will be obtained at designated time points, and serum samples will be obtained during the MMTT. Planned mechanistic studies include but are not limited to the following:

1. Immune cell phenotyping by flow cytometry: The markers that will be measured include those analyzed in the original TN-10 study and other markers that are suggested by

transcriptomic or other studies. Measurement of cell proliferation will be performed by staining with Ki67. The analysis will be done on PBMCs that will be frozen after collection and analyzed at a later time. Samples will be collected prior to the first dose of teplizumab and at the indicated intervals afterwards. In participants who received their first course of teplizumab during the TN-10 study, the results will be compared to the data from the first course of teplizumab administration.

2. The transcriptional signature of changes in immune cells with teplizumab treatment by single cell RNAseq or similar technologies: These changes will be compared to the findings from the previous administration of teplizumab in those who are receiving the drug for a second time.
3. The frequency and changes in phenotypes of diabetes antigen specific T cells: The frequency of these cells will be measured by Class I and/or Class II major histocompatibility complex (MHC) tetramer and T cell libraries. Frozen PBMCs will be used for this analysis.
4. Metabolic function including glucose tolerance, patterns and magnitude of endogenous cell responses, and other markers of β cell stress and death.
5. Analysis of changes in peripheral blood cells: The results of the CBC and differential tests will be used.
6. Anti-drug antibodies and effects of these antibodies on responses to teplizumab: The titers of anti-drug antibodies and presence of neutralizing antibodies will be measured in samples collected before and after teplizumab administration. The presence or absence of these antibodies and the changes in immune cells will be analyzed.
7. Epigenomic analysis of immune cell subsets: This analysis may involve techniques such as ATACseq will be performed on frozen cells and will be conducted after the initial transcriptomic studies.

8.4. Safety Assessments

Safety assessments include clinical safety laboratory tests, AE assessments, and pregnancy monitoring. Planned time points for all safety assessments are listed in Section 1.3.

8.4.1. Adverse Events and Serious Adverse Events

See Appendix 3 for the definitions of AEs, SAEs, and reporting instructions.

AEs will be reported by the participant or, when appropriate, by a caregiver, surrogate, or the participant's guardian or legally authorized representative.

Throughout the study, the investigator must record all AEs, including assessment of relatedness and severity (according to the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE]). The investigator should treat participants with AEs appropriately and observe them at suitable intervals until the events resolve or stabilize.

8.4.1.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the signing of the informed consent form (ICF) until the follow-up visit at the time points specified in Section 1.3.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.1.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and AEs of special interest (AESI, as defined in Section 10.3.3), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Appendix 3 in Section 10.3.

8.4.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal and regulatory obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

For all studies, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.2. Clinical Safety Laboratory Assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed.

The investigator should report any clinically relevant changes during the study as AEs. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

8.4.3. Physical Examinations

A complete physical exam includes evaluation of general appearance, head, eyes, ears, nose, and throat evaluation, neck palpation for thyroid, lymphadenopathy and tenderness, auscultation of the heart, lungs and abdomen, palpation of abdomen, evaluation of extremities and skin, and gross neurologic evaluation of strength, sensation and balance.

A partial physical examination includes general appearance, head, eyes, and throat evaluation, neck palpation for thyroid, lymphadenopathy and tenderness, auscultation of the heart, lungs and abdomen, palpation of abdomen, evaluation of extremities and skin.

Weight and height will be measured using calibrated scales. At each measurement, participants will be instructed to remove shoes and outdoor apparel and gear. Details on how to conduct these measurements will be provided to sites.

8.4.4. Vital Signs and Infusion Reaction Monitoring

The following vital signs will be measured at time points indicated in the Schedule of Events (Section 1.3):

- Temperature
- Pulse/heart rate
- Respiratory rate
- Blood pressure

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

On dosing days, vital signs should be measured at pre-dose and at approximately 15 minutes after the start of the infusion, at the end of infusion (approximately 30 minutes), and at 60 minutes after the end of the infusion.

Participants are to be monitored for signs or symptoms of infusion reactions. These include but are not limited to fever, chills, headache, nausea, vomiting, infusion-site pain, anaphylaxis, wheezing, dyspnea, urticaria, and hypotension. If there are signs or symptoms of infusion reaction in a participant during the 60-minute post-infusion observation period, the participant should have vital signs assessed and continue to be observed until the reaction is resolved.

8.4.5. Pregnancy

Pregnant and lactating women will not be included in the study. Females of childbearing potential must have a negative pregnancy test prior to enrolling in the study and will be required to use a reliable and effective form of birth control during the study. Male participants will also be required to prevent pregnancy in their partners. At every study visit the sexual activity of participants of reproductive age will be re-assessed. If a participant who was previously sexually inactive becomes sexually active, s/he will be counseled about the need to use a reliable and effective form of birth control. Female participants of childbearing potential will also be required to undergo urine pregnancy tests at regular intervals including prior to teplizumab administration. A positive pregnancy test will result in withholding scheduled drug infusion, and if confirmed, lead to study drug discontinuation.

All pregnancies that are identified during the study must be followed to its termination or delivery, and the outcome of each pregnancy must be reported. The investigator should be informed immediately of any pregnancy whether occurring in a female participant or the female partner of a male participant. The investigator should report all pregnancies within the same time frame (24 hours) as SAEs, using the Pregnancy report form.

8.5. Pharmacokinetics and Immunogenicity

Blood samples will be obtained to measure teplizumab trough levels and anti-drug antibodies at time points indicated in Section 1.3. Instructions for sample processing, handling, and shipping will be described in the Laboratory Manual.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetic information about TN-10 participants has already been obtained. There are no additional genetic studies planned.

9. Statistical Considerations

9.1. Statistical Hypotheses

There is no formal hypothesis to be tested in this study, whose primary objective is to evaluate the safety of teplizumab administration in participants of the TN-10 study who have developed clinical T1D. For the secondary endpoints, it is proposed that teplizumab treatment will reduce the loss of beta cell function (as measured by C-peptide) and will increase the frequency of exhausted T cells, TIGIT+KLRG1+CD8+ T cells, compared to baseline (at the start of study drug administration).

9.2. Sample Size Determination

The sample size will include a maximum of 33 participants who were free of clinical T1D at the conclusion of the TN-10 study.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Enrolled	All participants who sign the informed consent and/or assent
ITT	All participants who receive at least one dose of the study drug
Safety	All participants who receive at least 1 dose of the study drug and has at least one post-treatment observation

9.4. Statistical Analyses

The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the primary and secondary endpoints

9.4.1. Primary Endpoint: Safety

Safety variables will be presented descriptively. Details will be described in the Statistical Analysis Plan (SAP).

9.4.2. Secondary Endpoints

The effects of teplizumab treatment on the level of C-peptide measured during the MMTT will be evaluated and compared to the results with historical control data. The HbA1c levels and insulin use will be described descriptively. The frequency of exhausted T cells (CD8+ TIGIT+ KLRG1+ T cells), including the effect of anti-drug antibodies, will be described descriptively.

Additional analyses may be performed and will be specified in the SAP.

9.4.3. Handling Missing/Discontinued Participants

An intent-to-treat (ITT) approach will be used. Participants will not be replaced. All data acquired prior to termination for the reasons outlined below will be included in the analyses unless the participant withdraws consent. Every effort will be made to conduct the Early Termination visit with the participant and participants will be followed clinically until, if applicable, all AEs resolve.

9.5. Interim Analyses

An interim analysis is not planned.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Study-Specific Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each participant, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically participants 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to participants who have provided consent (and assent as applicable) refers to the participants and his or her parent(s) or the participant's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parents still want them to participate.

10.1.2. Investigator Responsibilities

The Investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

10.1.3. Regulatory and Ethical Considerations

Before the start of the study, the Investigator (or Sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

10.1.4. Informed Consent Process

Each participant and a legally acceptable representative must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) and assent form that is/are used must be approved by both the Sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before enrollment in the study, the Investigator or an authorized member of the study-site personnel must explain to potential participants and their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the Investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized Sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF/assent, the participant and legally acceptable representative are authorizing such access. It also denotes that the participant

agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations.

The participant and legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, assent/consent should be appropriately recorded by means of the participant's and his or her legally acceptable representative's personally dated signature. After having obtained the assent/consent, a copy of the ICF must be given to the participant and his or her legally acceptable representative.

If the participant or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the assent/ICF after the oral consent of the participant or legally acceptable representative is obtained.

10.1.5. Data Protection

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. The objectives of the study and the nature and detail of the personal data to be recorded by the Sponsor as a consequence of study participation will be explained to each study participant (or their legally acceptable representative) in the ICF and during the consent process.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. In Europe the Study will be conducted in compliance with Regulation (EU) 2016/679 “General Data Protection Regulation”. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to participants’ personal data shall be approved by the local IEC/IRB and shall agree to keep the participants’ personal data confidential.

The informed assent/consent obtained from the participant and his or her legally acceptable representative shall include explicit consent for the processing of personal data and for the Investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory authority inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request access to his or her personal data and the right to request rectification of any data that are not correct or complete. Details of which party to contact in respect of such requests shall be included in the ICF and in the consent process. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

In addition to these rights, a participant may restrict the processing of incorrect data, request a copy of the data or ask for them to be transferred to a third party (portability). A participant can also withdraw consent on the data, in which case no further information about the participant will be collected from that moment onward.

Any limitation placed upon the participant's right to erasure of their personal data from study records resulting from the need to conduct the study in compliance to locally applicable regulations and laws shall be explained in the ICF and in the consent process.

Exploratory research is not conducted under standards appropriate for the return of data to participants. In addition, the Sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not necessarily be returned to participants or Investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.1.5.1. Sample and Data Storage

Samples collected from participants in this study may be stored for up to 15 years or more (or according to local regulations) for additional research. Samples can be used to understand the effects of teplizumab on Type 1 diabetes, differential drug responders, and to develop tests/assays related to teplizumab or other autoimmune conditions. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research.

10.1.5.2. Use of Information and Publication

All information, including but not limited to information regarding teplizumab or the Sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the Sponsor to the Investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the Sponsor. The Investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the Sponsor's prior written consent.

The Investigator must agree to send to the Sponsor for review all manuscripts, abstracts and presentations using data from this study prior to their submission for publication. The Sponsor reserves the right to delete from such materials any part or parts deemed to be confidential or proprietary.

The Investigator understands that the information developed in the study will be used by the Sponsor in connection with the continued development of teplizumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide the Sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the Sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating Investigator. Results of exploratory analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the Investigator as provided for below) shall be the property of the Sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the Sponsor shall have the right to publish such primary (multicenter) data and information without approval from the Investigator. The Investigator has the right to publish study site-specific data after the primary data are published. If an Investigator wishes to publish information from the study, a copy of the manuscript must be provided to the Sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the Sponsor in writing, the Investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the Sponsor will review these issues with the Investigator. The Sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, Investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the Sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

10.1.6. Registration of Clinical Studies and Disclosure of Results

The Sponsor will register and disclose the existence of, and the results of clinical studies as required by law.

10.1.7. Required Pre-study Documentation

The following documents must be provided to the Sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the Principal Investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an Investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of Investigator (eg, Form FDA 1572), if applicable
- Documentation of Investigator qualifications (eg, curriculum vitae)
- Completed Investigator financial disclosure form from the Principal Investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the Sponsor before enrollment of the first participant:

- Completed Investigator financial disclosure forms from all sub-investigators
- Documentation of sub-investigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable

Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

10.1.8. Monitoring

The Sponsor or designee will use a combination of monitoring techniques (eg, central, remote, or on-site monitoring) to monitor this study.

The Sponsor or designee will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the Sponsor and study-site personnel and are accessible for verification by the Sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The Sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the Investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the Sponsor or designee as requiring central review.

10.1.9. Data Quality Assurance

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the Investigator and study-site personnel before the study, and periodic monitoring visits by the Sponsor, and direct transmission of clinical laboratory data from a central laboratory into the Sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

Clinical monitors will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the Sponsor; any discrepancies will be resolved with the Investigator or designee, as appropriate.

10.1.10. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the Investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirement for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria, that specify a need for documented medical history is the complete history of medical notes at the site.

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol.

10.1.11. Case Report Form Completion

Study-specific CRFs are prepared for each participant in electronic format.

Electronic Data Capture (EDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto electronic CRFs (eCRF) via the secure EDC system in accordance with the study calendar, and within the timeframe agreed upon between the Sponsor and the study site.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

When necessary, queries will be generated in the EDC system. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study personnel can make corrections in the EDC system at their own initiative or as a response to a query (from the EDC system).
- Sponsor or Sponsor delegate can generate a query for resolution by the Investigator and study-site personnel.

All CRF entries, corrections, and alterations must be made by the Investigator or authorized study-site personnel. The Investigator must verify that all data entries in the CRF are accurate and correct. Investigator will review, sign, and date completed CRFs at regular intervals as determined by the Sponsor.

10.1.12. Record Retention

In compliance with the ICH/GCP guidelines, the Investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The Investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the Investigator/institution must permit access to such reports.

10.1.13. Study Completion/Termination

10.1.14. Study Completion/End of Study

The study will be considered to have completed when the database is locked after the last participant's last visit.

The Investigator will notify the IRB/IEC when the study has been completed.

10.1.15. Study Termination

The Sponsor reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator

Discontinuation of further study drug development

10.1.16. On-Site Audits

Representatives of the Sponsor's clinical quality assurance department or designee may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The Investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the Sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The Investigator should immediately notify the Sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.2. Appendix 2: Clinical Laboratory Tests Performed Locally

The following clinical laboratory assessments will be performed locally during the study as described in the Schedule of Events (Section 1.3):

- Chemistry (sodium, potassium, chloride, CO2, glucose, BUN, creatinine)
- Liver function tests (ALT, AST, LDH, alkaline phosphatase, total protein, albumin, total and direct bilirubin). Prior to each infusion, MMTT will be run locally in participants with Gilbert's syndrome.
- Hematology (complete blood count with differential and platelets)
- HbA1c
- Purified protein derivative (PPD) or IGRA test for TB
- Urine pregnancy test for women of childbearing potential (WOCBP)
- Antibodies to HIV, hepatitis B (anti-hepatitis B core antibody, hepatitis B surface antigen), hepatitis C (HCV)
- Cytomegalovirus antibodies (CMV IgG and IgM).,
- Epstein-Barr virus antibodies (EBV IgG, IgM and EBNA). The Investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. • Hypoglycemia and hyperglycemia will be reported as adverse events only in the case of requiring the assistance of others due to loss of consciousness or diabetic ketoacidosis (DKA).
Unexpected AE: • An adverse event is considered unexpected when the nature (specificity) or severity of the event is not consistent with the risks described in the Investigator's Brochure or the informed consent document.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of AESI

The following types of AEs are considered AESIs:

- All infections: viral, fungal, bacterial
- Acute mononucleosis-like illness (eg, fever, pharyngitis, lymphadenopathy)
- CMV viremia defined using DNA PCR testing and >10,000 copies per mL serum or 106 cells
- EBV viremia defined using DNA PCR testing and >10,000 copies per mL serum or 106 cells
- Herpes zoster or other conditions related to VZV
- Primary infection with or reactivation of latent tuberculosis
- Infections requiring IV antibiotic treatment
- Demyelinating diseases
- Malignancies including lymphomas
- Severe hypoglycemic episodes that require assistance by another individual through the administration of oral or parenteral dextrose, glucagon or intervention
- ≥ Grade 3 liver function abnormalities (AST, ALT, bilirubin)
- ≥ Grade 3 thrombocytopenia (platelet counts less than 50,000/μL)
- ≥ Grade 3 allergic/hypersensitivity reaction (anaphylaxis)
- ≥ Grade 3 Rash

- ≥ Grade 3 cytokine-release syndrome
- ≥ Grade 4 neutropenia (<500 PMN/µL on 2 consecutive evaluations performed on different days)

10.3.4. Reporting and Follow-Up of AE and/or SAE

AE and SAE Reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, Investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

The determination of seriousness, severity and causality must be made by the physician Investigator who is qualified to review adverse event information, provide a medical evaluation of adverse events, and classify adverse events based upon medical judgment.

An adverse event is any untoward medical occurrence in a clinical study participant from the time they formally agree to participate in the study (eg, by providing informed consent/assent) through their last study contact (eg, last visit or status update). An adverse event does not necessarily have a causal relationship with the study drug. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a study drug (investigational or non-investigational product), whether or not related to that study drug (investigational or non-investigational product).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

A treatment-emergent adverse event (TEAE) is defined as an AE that occurs after the first dose of study drug administration (Day 1) through the end of the study or early termination.

The Investigator must follow all SAEs (including serious AESIs) until resolution even if this extends beyond the study-reporting period. Resolution of a SAE is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic. At any time after completion of the study, if an Investigator becomes aware of a serious adverse event that s/he suspects is related to study drug, the Investigator should report the event to the Pharmacovigilance contact.

These events will be captured on the CRF and reported to the Sponsor as described in Section 8.4.1.1. Any event that meets serious adverse event criteria will be reported to the Sponsor within the appropriate timeline as described in Section 8.4.1.4.

Events will be assessed and reported consistent with the ICH Guideline for Good Clinical Practice and per the guidance of the DHHS Office for Human Research Protections (OHRP).

Event outcome and other follow-up information regarding the treatment and resolution of the event will be obtained and reported when available, if not known at the time the event is initially reported. The follow-up information should contain sufficient detail to allow for a complete medical assessment of the case and an independent determination of possible causality.

AESIs should be reported according to the requirements for SAEs.

Assessment of Severity

An assessment of severity grade for each AE will be made by the site Investigator according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 5.0. This document (referred to herein as the "CTCAE V5.0") provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all AEs. The Investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

Adverse events will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0:

- Grade 1 = Mild adverse event.
- Grade 2 = Moderate adverse event.
- Grade 3 = Severe adverse event.
- Grade 4 = Life-threatening or disabling adverse event.
- Grade 5 = Death

Assessment of Causality

The Investigator is required to provide an assessment of causality or relationship of adverse events to the study drug based on 1) temporal relationship of the event to the administration of study drug; 2) whether an alternative etiology has been identified; and 3) biological plausibility. The causality assessment categories that will be used for this study are described below.

Causality assessments considered **not** related to study drug:

- Unrelated: The event is related to an etiology other than the study drug (the alternative etiology must be documented in the participant's medical record).
- Unlikely: The event is unlikely to be related to the study drug and likely to be related to factors other than study drug.

Causality assessments considered **related** to study drug:

- Possible: There is an association between the event and the administration of the study drug and there is a plausible mechanism for the event to be related to study drug; but there may also be alternative etiology, such as characteristics of the participant's clinical status or underlying disease.
- Probable: There is an association between the event and the administration of study drug, a plausible mechanism for the event to be related to the study drug and the event could not be reasonably explained by known characteristics of the participant's clinical status or an alternative etiology is not apparent.

Definite: There is an association between the event and the administration of study drug, a plausible mechanism for the event to be related to the study drug and causes other than the study drug have been ruled out and/or the event re-appeared on re-exposure to the study drug.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female:

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement [insert threshold if required (>40 IU/L or mIU/mL) or remove to allow for flexibility with different local thresholds for defining postmenopausal state] is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive [study intervention].

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within [24 hours] of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within [24 hours] of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study [will discontinue study intervention or be withdrawn from the study] OR [may request continuation of study intervention.

10.5. Appendix 5: Abbreviations

ADA	American Diabetes Association
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-versus-concentration curve
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CD	cluster of differentiation
CMV	cytomegalovirus
CRF	case report form(s) (paper or electronic as appropriate for this study)
CRS	cytokine-release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DCCT	Diabetes Control and Complications Trial
DKA	diabetic ketoacidosis
DNA	deoxynucleic acid
DPT-1	Diabetes Prevention Trial – Type 1
EBNA	Epstein Barr nuclear antigen
EBV	Epstein-Barr virus
EDC	electronic data capture
ENDIT	European Nicotinamide Diabetes Intervention Trial
ET	early termination
Fc	fragment crystallizable region of an antibody/immunoglobulin molecule
FcR	receptor binding to the Fc component of antibody molecules
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator Brochure
ICF	informed consent form

ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGRA	interferon gamma release assay
IHSG	International Hypoglycaemia Study Group
IL	interleukin
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous(ly)
KD	kilodalton
LDH	lactate dehydrogenase
LFT	liver function test
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MMTT	mixed meal tolerance test
NAb	neutralizing antibody
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
PMN	polymorphonuclear leukocyte
PPD	purified protein derivative
PVC	polyvinyl chloride
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
T1D	type 1 diabetes
TN-10	Anti-CD3 Monoclonal Antibody (Teplizumab) for Prevention of Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus Trial
TB	tuberculosis
TCR	T cell receptor

TEAE	treatment-emergent adverse event
U	unit
ULN	upper limit of normal range
VZV	varicella zoster virus
WBC	white blood cell
ZnT8	zinc transporter 8

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): [redacted]

Organization: Provention Bio, Inc

Signature: [redacted] Date: [redacted]

(Day Month Year)

Note: If the address or telephone number of the Investigator changes during the course of the study, written notification will be provided by the Investigator to the Sponsor, and a protocol amendment will not be required.